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# Matrix Metalloproteinases and Protein Tyrosine Kinases

## Potential Novel Targets in Acute Lung Injury and ARDS

*Yael Aschner, MD; Rachel L. Zemans, MD; Cory M. Yamashita, MD; and Gregory P. Downey, MD, FCCP*

Acute lung injury (ALI) and ARDS fall within a spectrum of pulmonary disease that is characterized by hypoxemia, noncardiogenic pulmonary edema, and dysregulated and excessive inflammation. While mortality rates have improved with the advent of specialized ICUs and lung protective mechanical ventilation strategies, few other therapies have proven effective in the management of ARDS, which remains a significant clinical problem. Further development of biomarkers of disease severity, response to therapy, and prognosis is urgently needed. Several novel pathways have been identified and studied with respect to the pathogenesis of ALI and ARDS that show promise in bridging some of these gaps. This review will focus on the roles of matrix metalloproteinases and protein tyrosine kinases in the pathobiology of ALI in humans, and in animal models and in vitro studies. These molecules can act independently, as well as coordinately, in a feed-forward manner via activation of tyrosine kinase-regulated pathways that are pivotal in the development of ARDS. Specific signaling events involving proteolytic processing by matrix metalloproteinases that contribute to ALI, including cytokine and chemokine activation and release, neutrophil recruitment, transmigration and activation, and disruption of the intact alveolar-capillary barrier, will be explored in the context of these novel molecular pathways. CHEST 2014; 146(4):1081-1091

**ABBREVIATIONS:** ALI = acute lung injury; ECM = extracellular matrix; EGFR = epidermal growth factor receptor; LPS = lipopolysaccharide; MMP = matrix metalloproteinase; NRTK = nonreceptor tyrosine kinase; PDGF = platelet-derived growth factor; PDGFR = platelet-derived growth factor receptor; PTK = protein tyrosine kinase; RTK = receptor tyrosine kinase; SFK = Src family kinase; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VILI = ventilator-induced lung injury

ARDS is characterized by progressive arterial hypoxemia, dyspnea, increased work of breathing, and respiratory failure.[1,2] The hallmarks of the clinical syndrome include bilateral radiographic infiltrates, hypoxemia, and decreased pulmonary compliance.[1,2] Histopathologically, ARDS is characterized by interstitial and alveolar edema, accumulation of inflammatory and RBCs in the alveolar spaces, denudation of the alveolar

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**AFFILIATIONS:** From the Division of Pulmonary, Critical Care, and Sleep Medicine (Drs Aschner, Zemans, and Downey), Departments of Medicine and Pediatrics, National Jewish Health, Denver, CO; Division of Pulmonary Sciences and Critical Care Medicine, Departments of Medicine (Drs Aschner, Zemans, and Downey) and Immunology (Dr Downey), University of Colorado Denver, Aurora, CO; and Department of Medicine (Dr Yamashita), University of Western Ontario, London, ON, Canada.

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**CORRESPONDENCE TO:** Gregory Downey, MD, FCCP, Academic Affairs, K701b National Jewish Health, 1400 Jackson St, Denver, CO, 80206; e-mail: downeyg@njhealth.org



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epithelium, and hyaline membrane formation. Proliferation of alveolar type 2 epithelial cells and fibroblasts and deposition of collagen with subsequent fibrosis (fibroproliferative ARDS) may occur in the subacute and chronic phases and is associated with increased morbidity and mortality.[3]

The definition of ARDS has been revised to reflect the degree of hypoxemia, dividing the spectrum of disease into mild, moderate, and severe, and allowing greater predictive power in terms of morbidity.[4] While the term acute lung injury (ALI) is no longer used clinically, animal models of ALI have been developed with many features in common with human ARDS. Thus, for the purposes of this review, ALI and ARDS will be used interchangeably to reflect their common pathophysiology.

ARDS can be associated with both direct (pneumonia, aspiration of gastric contents) and indirect (sepsis, trauma, multiple transfusions) injury to the lung. Sepsis is the most commonly associated clinical disorder, accounting for approximately 40% of ARDS cases.[5] ARDS results in a large burden of critical illness, with $>$200,000 cases annually in the United States and a mortality rate ranging from approximately 23% to 45%, depending on various factors, such as comorbidities.[4,6-8] Although most of those who survive the acute illness recover near-normal pulmonary function within 1 year,[2] many survivors suffer from long-term sequelae, including exercise limitation, physical and psychologic impairment, decreased quality of life, and increased costs and use of health-care resources.[9] However, while biomarkers that predict disease severity and prognosis are emerging,[10] additional markers are needed to identify patients with ARDS who may be at the highest risk for adverse outcomes and who might derive the greatest benefit from targeted therapeutic intervention.

The pathogenesis of ALI/ARDS is complex and involves an excessive and inappropriate inflammatory response resulting in damage to the alveolar-capillary barrier, accumulation of pulmonary edema fluid, and impaired removal of edema fluid and resolution of inflammation.[1,2] In the acute phase of lung injury, increased permeability of the alveolar-capillary barrier results in an influx of protein-rich edema fluid that contains large numbers of neutrophils, monocytes, and denuded epithelial cells, as well as proinflammatory mediators such as cytokines, proteinases, oxidants, and procoagulants[1,5] (Fig 1). Not only does epithelial injury contribute to the accumulation of edema fluid and generation of proinflammatory mediators, it also results in impaired surfactant production and function,[11] and abnormal fluid transport, resulting in impaired clearance of edema fluid.[5] One of the best characterized mechanisms of lung injury is via damage to the endothelium and epithelium by neutrophil-derived mediators, including proteinases and reactive oxygen species.[12,13] This damage includes endothelial and epithelial cell death and leads to increased permeability of the alveolar-capillary barrier.[12-14] Other mechanisms may also contribute to the development of ALI, including cytokine release,[15] dysregulation of the coagulation system,[16] and excess mechanical stretch, as in the case of ventilator-induced lung injury (VILI).[17,18]

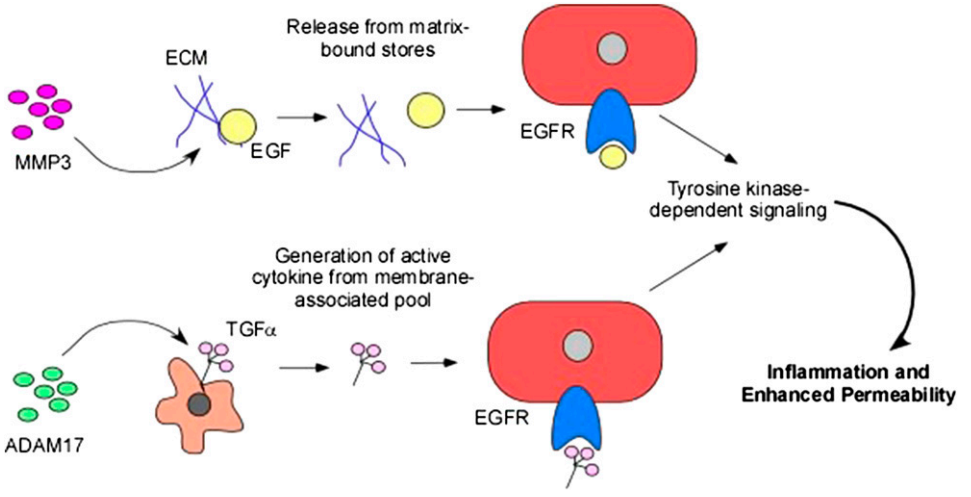


Figure 1 – *Coordinate roles of MMPs and tyrosine kinases in control of lung inflammation. MMPs can release cytokines and growth factors from pools bound to the ECM, leading to increased local and systemic levels of these mediators. EGF is used as an example of this mechanism. Additionally, MMPs and other proteinases can cleave membrane-bound molecules generating active mediators such as cytokines and growth factors that trigger tyrosine kinase-dependent signaling pathways. TGF-α is used as an example of this mechanism. ECM = extracellular matrix; EGF = endothelial growth factor; EGFR = endothelial growth factor receptor; MMP = matrix metalloproteinase; TGF = transforming growth factor.*

This review will focus on the roles of two classes of molecules that participate in the development of ALI: the matrix metalloproteinases (MMPs) and protein tyrosine kinases (PTKs), which are emerging as key participants in the pathogenesis of ARDS and represent potential targets for therapeutic intervention (Fig 1). While MMPs and PTKs have various independent functions, they have been shown to act coordinately and on common pathways, culminating in lung injury. As shown in Figures 1 and 2, mechanisms involving proteolytic processing of cytokines, growth factors, and receptors that lead to the recruitment and activation of immune cells, enhanced cytokine responses, and disruption of epithelial and endothelial barriers, represent potential avenues by which MMPs and PTKs contribute to lung injury in the context of ARDS.

## Introduction to MMPs

The MMPs compose a family of > 20 structurally related, zinc-dependent endopeptidases that can degrade collagen and other components of the extracellular matrix (ECM). MMPs are members of the metzincin subgroup of zinc proteinases, along with the adamalysins, which contain a similar metalloproteinase domain and can act on overlapping substrates, but differ from MMPs based on unique integrin-receptor binding disintegrin domains.[19] MMPs have been shown to play a critical role in physiologic tissue remodeling and wound repair.[20,21] MMPs can be produced by immune cells, fibroblasts, and epithelial cells, and are divided into subgroups based on their substrate specificity and structural properties: (1) gelatinases (MMP-2 and -9), (2) stromelysins (MMP-3, -10, and -11), (3) collagenases (MMP-1, -8, and -13), (4) matrilysins (MMP-7 and -26), and (5) membrane-type MMPs (MMP-14, -15, -16, -17, -24, -25).[22] In addition to their ability to degrade and remodel the ECM, MMPs can cleave nonmatrix molecules, resulting in alterations in cell-matrix and cell-cell interactions and activation or inactivation of cytokines, growth factors, and cell-surface receptors.[23] These pleiotropic activities allow MMPs to participate in inflammation, host defense, and repair of injured tissues.[24] MMPs have also been implicated in pathologic processes, including rheumatoid arthritis, cancer, and fibrosis of the liver, kidneys, heart, and lungs.[25-29] Recent evidence suggests that MMPs play a role in the pathogenesis of ALI/ARDS.

## MMP Levels Correlate With Risk and Severity of ARDS in Humans

Considerable clinical data have demonstrated associations between lung injury and increased levels of a variety of MMPs, including MMP-1, -2, -3, -7, -8, -9, -12 and -13 in BAL fluid.[30-34] Furthermore, BAL levels of MMP-2, -8, and -9 correlated with increased neutrophil counts, while MMP-1 and MMP-3 levels correlated with increased mortality, disease severity, and multiorgan failure. Thus, BAL or blood levels of individual or panels of MMPs may serve as markers of acute neutrophilic inflammation, while levels of other MMPs may provide further insight in terms of prognostic implications.[35,36]

## Cytokine and Chemokine Processing by MMPs

As noted, MMPs can regulate tissue injury and repair by altering the activity of nonmatrix proteins including cytokines, chemokines, and membrane receptors (Figs 1, 2). Multiple cytokines can be cleaved by MMPs, resulting in activation, inactivation, or alterations in bioavailability, which may contribute to further inflammation in the injured lung. For example, MMP-7 is required for shedding of membrane-bound tumor necrosis factor-α (Fig 2), a step that is obligatory for its innate biologic functions.[37] Similarly, transforming growth factor-β, which is increased in the BAL fluid of patients with ARDS and induces pulmonary edema in animal models of ALI,[38,39] can be activated by release from its latent complex by multiple MMPs, including MMP-2, -3, -9, and 14.[40-43] IL-1β may also be activated by proteolytic cleavage from an inactive precursor by MMP-2, -3, and -9.[44] Conversely, some of these same enzymes (MMP-1, -2, -3, and -9) can inactivate IL-1β by more extensive proteolytic cleavage.[44,45] Thus, MMPs can exert both positive and negative influences on inflammation.[46,47]

Neutrophil-mediated injury to the alveolar epithelium and endothelium are central to the pathogenesis of ARDS. Several studies have suggested that MMPs play a role in neutrophil recruitment and, thus, promote lung injury. For example, mice genetically deficient in MMP-3 and MMP-9 were protected from lung injury in an immune complex model of ALI.[48] MMP-3-deficient mice also exhibited diminished neutrophil recruitment, a pattern that was not seen in MMP-9-deficient mice, highlighting that individual MMPs act by different mechanisms in the pathogenesis of ALI.[48] Mice deficient in MMP-1 were also protected from ALI induced by immune complexes or intratracheal instillation of MIP-2, a neutrophil chemoattractant.[49] Finally, MMP-3-deficient mice were protected from bleomycin-induced pulmonary fibrosis,[50] a model that includes an early acute inflammatory response associated with ALI.[51]

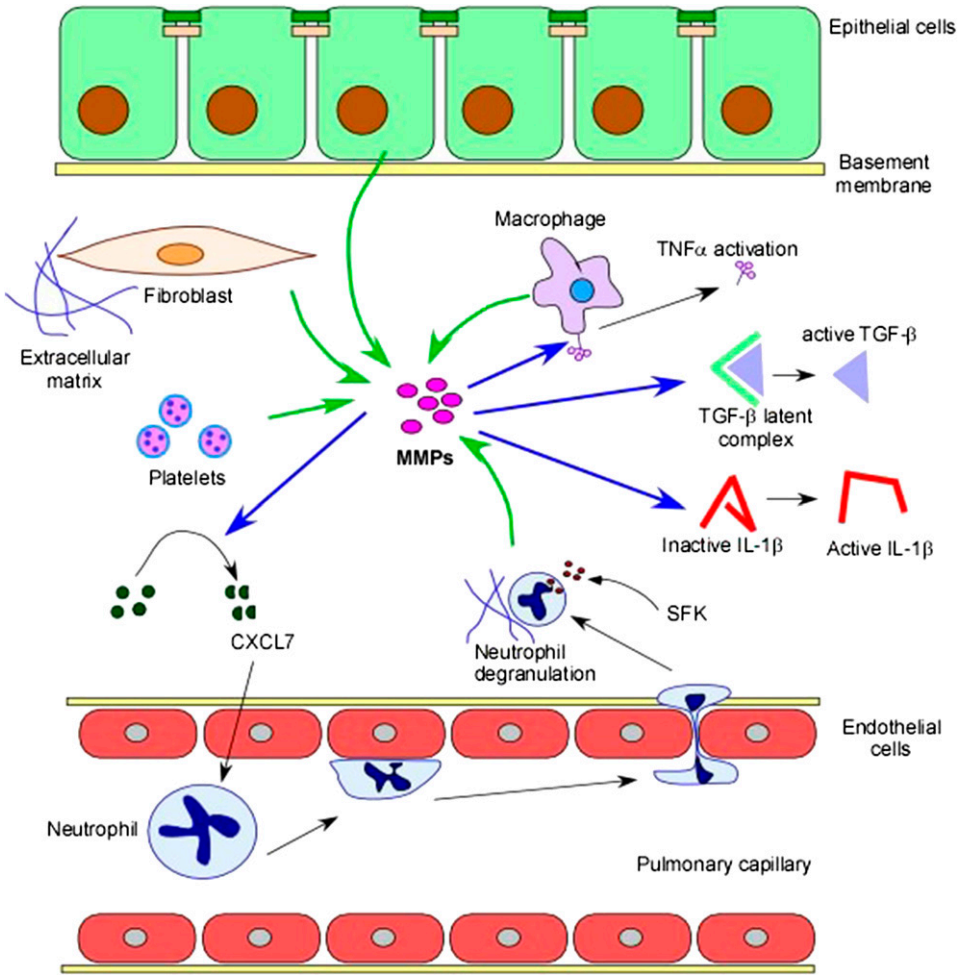


Figure 2 – *Regulation of lung inflammation. MMPs and protein tyrosine kinases (PTKs) can influence inflammatory responses in several ways. MMPs can be secreted from various cell types, including fibroblasts, macrophages, platelets, and epithelial cells (green arrows). MMPs can act on multiple targets (blue arrows). MMPs can cleave chemokines, such as CXCL7, resulting in enhanced chemotactic responses. They can also proteolytically process cytokines, leading to their activation, including TNF-α, TGF-β, and IL-1β. MMPs can also proteolytically cleave and activate receptor tyrosine kinases) and/or their ligands, triggering downstream proinflammatory signaling pathways. PTK signaling, including through SFKs, can result in proinflammatory responses such as degranulation of recruited neutrophils. SFK = Src family kinase; TNF = tumor necrosis factor. See Figure 1 legend for expansion of other abbreviations.*

While the mechanisms by which MMPs induce neutrophil recruitment into the lung remain unclear, several possibilities can be inferred from studies investigating their roles in disease models of the lung and other organs. For example, MMP-7 released from wounded epithelial cells cleaves a complex of KC/syndecan-1, allowing the complex to cross the epithelium into the alveolar space and establish a chemotactic gradient for neutrophils.[52] In IL-1β-stimulated intestinal epithelial cells, proteolytic cleavage of platelet basic protein by MMP-3 yielded the active neutrophil chemokine CXCL7.[53] Similarly, MMP-8 and MMP-9 can proteolytically activate CXCL5 and CXCL8, respectively,[46] while MMP-3 is capable of generating a macrophage chemotactic factor in the setting of disc degeneration.[37] Other studies have shown that MMPs can influence leukocyte trafficking (Fig 3) by mechanisms such as MMP-mediated proteolysis of cryptic ECM sites possessing chemotactic properties, release of chemokines from the ECM resulting in chemokine gradients, and degradation of ECM-derived barriers allowing for passage of neutrophils into various physiologic compartments.[46,47]

## Breach of the Epithelial Barrier

Inflammatory injury to the alveolar epithelium, endothelium, and basement membranes is integral to the pathogenesis of ARDS. An intact alveolar-capillary barrier can be disrupted by degradation of the basement membrane or destruction of interendothelial or interepithelial junctions or anchoring proteins.[54] Both MMP-2

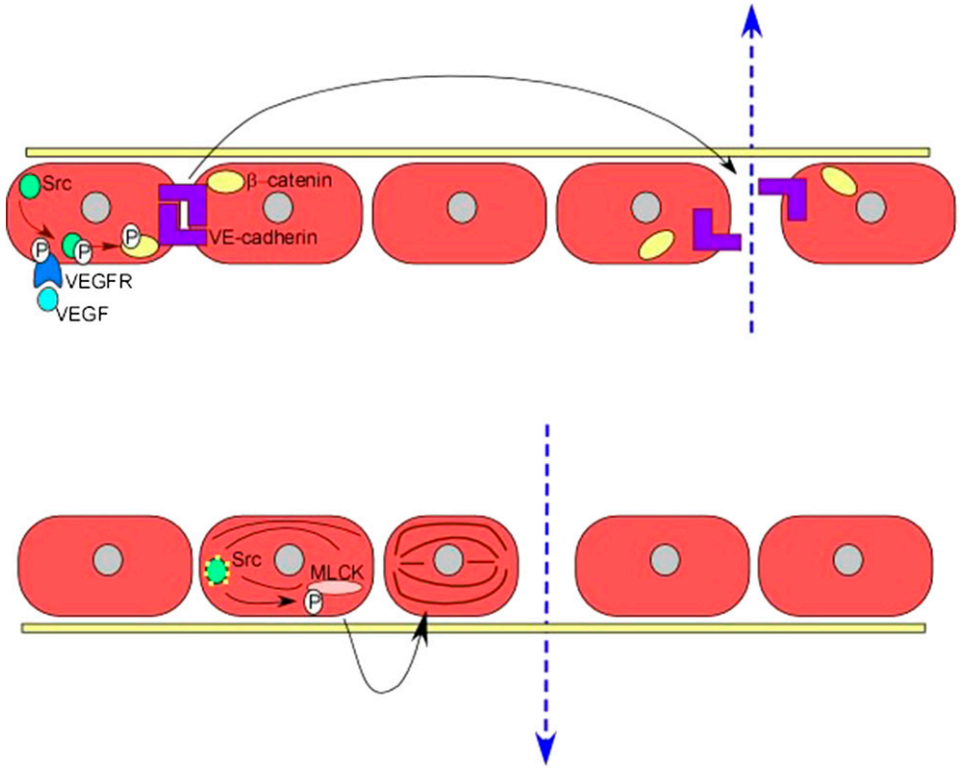


Figure 3 – *Increased vascular permeability. Protein tyrosine kinase signaling enhances vascular permeability in several ways. Signaling via receptor tyrosine kinases and nonreceptor tyrosine kinases, including VEGFR and Src, results in phosphorylation of β-catenin and subsequent dissociation of VE-cadherin homodimers, which loosens cell-cell contacts. Src also phosphorylates and activates MLCK, causing alterations in the cytoskeleton and changes in endothelial cell structure and shape, leading to increased endothelial permeability. MLCK = myosin light chain kinase; VE = vascular endothelial; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.*

and MMP-9 can degrade type 4 collagen (Fig 4), the main component of basement membranes.[55] Markers of basement membrane disruption are present in the BAL fluid of patients with ARDS and levels of these markers correlate positively with levels of MMP-2 and MMP-9.[31] Additionally, MMP-3 can cleave E-cadherin, an important component of interepithelial junctions needed for cell-cell contact and maintenance of an intact alveolar-capillary barrier.[56]

## Ventilator-Induced Lung Injury

In VILI, excessive mechanical stress induces pro-inflammatory responses resulting in adverse patient outcomes, while low tidal volume, lung-protective ventilator strategies have been shown to attenuate this phenomenon.[18,57-59] MMPs released in the setting of mechanical stress may mediate some of the injurious effects of VILI by promoting acute inflammatory responses. For example, MMP-8-deficient mice subjected to injurious ventilation demonstrated enhanced gas exchange, decreased lung permeability and edema, and reduced levels of inflammation, as compared with wild-type control mice.[60] Conversely, MMP-9-deficient mice exhibited more severe VILI compared with wild-type control mice, perhaps attributable to the role that MMP-9 plays in control of release and/or activation of protective cytokines.[61] Such studies demonstrating potentially divergent roles of MMPs in the context of VILI underscore the complexity of these enzymes in pathogenesis of lung injury.

## Lung Repair After Acute Injury

In addition to the reported effects of MMPs in the acute injury phase, there is also evidence supporting a role for these enzymes in the wound healing and repair phases of ARDS. Repair of alveolar epithelial damage involves spreading and migration of adjacent alveolar type 2 cells along a provisional matrix, with subsequent proliferation and differentiation to alveolar type 1 cells.[62] MMP-7 has been implicated in this process; overexpression of MMP-7 resulted in enhanced epithelial cell migration during wound repair.[35,63] In bleomycin and wounded tracheal explant models, MMP-7 deficiency resulted in decreased E-cadherin shedding, a process that loosens cell-cell contacts and is needed for cell migration during

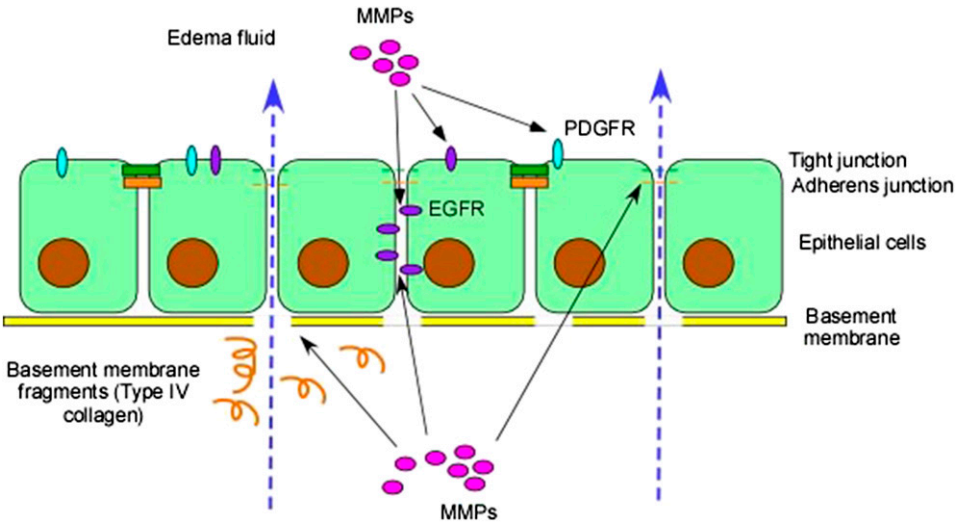


Figure 4 – *Breach of epithelial barrier. MMPs can disrupt various components of the epithelial barrier, allowing for transcellular passage of edema fluid and proteins, including proteinases such as MMPs. MMPs can also cleave the basement membrane, resulting in release of type 4 collagen fragments; and disrupt tight and adherens junctions, loosening cell-cell contacts. MMP secretion can also activate various RTKs, such as EGFR and PDGFR, leading to proinflammatory downstream signaling. PDGFR = platelet-derived growth factor receptor; RTK = receptor tyrosine kinase. See Figure 1 legend for expansion of other abbreviations.*

wound repair.[63] In vitro, MMP-9 activity correlates with a migratory phenotype that is essential for wound healing.[64]

In summary, MMPs are capable of degrading the ECM, and also function to regulate cell behavior through proteolytic processing of numerous cytokines and growth factors that play a role in the development of and response to injury and inflammation. Multiple in vitro and in vivo studies have shown that MMPs are central in the pathogenesis of ALI through processing and activation of cytokines and barrier disruption, while also playing a role in the resolution of lung injury.

In addition to their direct effects, MMPs interact with other signaling pathways involved in ALI. Among these pathways are those regulated by protein tyrosine kinases (PTKs). MMPs can activate these pathways by enhancing the bioavailability of ligands through ECM processing or cleavage of non-ECM molecules.[65] Alternatively, MMP expression and secretion can be increased as a downstream consequence of various signaling cascades that are controlled by the action of a variety of PTKs. Even when PTKs act independently of MMP-mediated actions, the final pathologic outcomes are often similar, resulting in inflammatory cell recruitment and barrier dysfunction, which ultimately culminate in development of lung injury. The role of PTKs in ALI and ARDS, both dependent and independent of MMPs, will be addressed in the following sections.

## Introduction to PTKs

PTKs are a family of enzymes that catalyze the reversible phosphorylation of tyrosine residues on substrate proteins. Phosphorylation can occur as an autophosphorylation event or as phosphorylation of a downstream signaling protein.[66] Through this process, PTKs are able to regulate diverse physiologic cellular functions, including proliferation, differentiation, migration, and metabolism.[67] PTKs are subdivided into two groups: receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (NRTKs). RTKs include receptors for many growth factors, such as platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor receptor (VEGFR). NRTKs can transmit signals downstream of RTKs, as well as other cell surface receptors.[66] The catalytic activity of both RTKs and NRTKs is tightly regulated, although overexuberant responses have been shown to play a role in pathologic states such as ALI.[68] The mechanisms underlying PTK effects in ALI include neutrophil chemoattraction and activation, and modulation of endothelial permeability. The latter may occur by decreased adhesion between adjacent endothelial cells at sites of intercellular junctions, allowing for passage of edema fluid and protein into the interstitial space. Increased adhesion of inflammatory cells may also occur, facilitating leukocyte recruitment at sites of injury.[69] These physiologically important responses are controlled by PTKs and will be addressed in more detail later.

## Src and Src Family Kinases

The Src family kinases (SFKs) compose the largest subfamily of NRTKs with nine members, including Src, Fyn, Yes, Yrk, Blk, Fgr, Hck, Lck, and Lyn.[66] SFKs play a critical role in the regulation of inflammatory responses, including ALI.[68] Animal models of oxidant- and lipopolysaccharide (LPS)-induced lung injury have revealed increased Src activity.[70,71] In rodent models of ALI, Src inhibitors attenuated lung injury, with decreased pulmonary neutrophil sequestration, capillary permeability, and cytokine and chemokine levels.[72,73] Additionally, mechanical stress (eg, VILI) results in SFK activation.[74,75] Several molecular mechanisms underlie the role SFKs play in promoting lung injury, including recruitment and activation of immune cells and regulation of vascular permeability.[68] SFKs and cytoskeletal proteins interact to influence neutrophil adhesion and activation.[76] SFK activation correlates with neutrophil adhesion following $\beta_2$-integrin-dependent tyrosine phosphorylation[77] and neutrophils from Hck and Fgr double-knockout mice exhibited an impaired adhesion-dependent respiratory burst.[78] Thus, SFKs are required for adhesion and spreading of neutrophils on ECM, leading to enhanced activation. SFKs are also required for adhesion-dependent neutrophil degranulation with release of a diverse array of powerful proteinases that can damage the lung.[79]

In addition to enhancing inflammatory cell responses, SFKs also regulate structural alterations in the endothelium affecting vascular permeability by phosphorylation of myosin light-chain via regulation of myosin light-chain kinase activity.[68] Src may also phosphorylate the junctional proteins VE-cadherin and β-catenin, promoting dissociation from their cytoskeletal anchors and resulting in endothelial barrier dysfunction (Figs 2, 3), which may contribute to pulmonary edema.[68] Importantly, Src inhibitors attenuated the increased lung permeability in animal models of ALI.[71]

## VEGF Receptors

VEGFR-2 mediates most of the effects of vascular endothelial growth factor (VEGF) on endothelial cells, including cell proliferation, angiogenesis, and vascular permeability. VEGFR-2 expression is increased under conditions of hypoxia, a hallmark of ARDS.[80] Stimulation of endothelial cells with MMP-1 increases the expression of VEGFR-2,[81] and a subset of MMPs can cleave matrix-bound VEGF to release soluble fragments.[82] Interestingly, VEGF stimulation increases secretion of MMP-1, -3, -9, and -13, which may provide the basis for a feed-forward loop.[83,84]

Ligand binding to VEGFR-2 results in activation of focal adhesion-associated kinases, including p38 MAPK and focal adhesion kinase (a tyrosine kinase) with subsequent tyrosine phosphorylation of paxillin, leading to endothelial cell migration.[85] In addition, interactions with Src and Yes may mediate VEGF-induced vascular permeability.[86] Clinically, patients with ARDS have been shown to have increased plasma levels of VEGF compared with normal control subjects or those at risk for ARDS.[87]

## Human EGFRs

The EGFR family of RTKs regulates airway and alveolar epithelial barrier function during injury and repair. EGFR signaling can be protective or injurious depending on the context, degree of activation, and experimental model.[88] EGFR ligand shedding is induced in the setting of injury (scratch or mechanical stress), resulting in EGFR activation,[89,90] in turn promoting cell proliferation, spreading, and motility.[91,92] Cell spreading in response to IL-1β-dependent activation of EGFR can enhance repair of wounded epithelium.[93] Conversely, EGFR promotes lung injury in animal[94] and cell culture[95] models of VILI; inhibition of HER2, a member of the EGFR family, in a murine model of ALI attenuated lung injury.[96] Administration of exogenous EGFR, however, did not recapitulate injury, suggesting that EGFR is necessary but not sufficient to induce lung injury.[94] EGFR-related lung injury may be mediated by rearrangement of apical junctional complex proteins, resulting in disruption of cell-cell adhesions and leading to epithelial barrier dysfunction.[97,98] EGF can also induce the expression of various MMPs, which, in turn, promote lung injury.[99] In lung interstitial smooth muscle cells, EGFR transactivation mediated by ADAM17-dependent shedding of ligands (Fig 1) is necessary for the development of acute pulmonary inflammatory responses, such as edema formation and neutrophil recruitment.[100]

## Eph Receptors

The Eph receptor tyrosine kinases are cell-surface molecules activated by ephrin ligands that modify cytoskeletal organization and cell-cell and cell-surface adhesion. Signaling through these receptors results in activation of multiple downstream pathways, including Src family kinases, MAPK, and chemokine signaling pathways.[69,101] EphA2 receptor and its ligand, ephrin-A1, have been implicated in the pathogenesis of ALI, primarily by inducing endothelial permeability.[102] This may occur via activation of a RhoA-GTPase

signaling pathway, resulting in destabilization of VE-cadherin-mediated endothelial cell-cell adhesion.[103] In addition, Eph2A mediated upregulation of ICAM-1 may result in changes in endothelial cell cytoskeletal structure, ultimately resulting in leukocyte adhesion and increased vascular leak.[104] In vivo, biphasic downregulation and upregulation of EphA2 and ephrin-A1 have been shown in LPS-injured rat lungs,[105] and EphA1 receptor expression was increased in a model of hypoxia.[102] Administration of ephrin-A1 in rats resulted in endothelial barrier disruption,[102] while EphA2 receptor inhibition reduced lung edema and albumin extravasation.[106] In addition, EphA2 knockout mice were protected from bleomycin-induced lung injury.[107]

## Platelet-Derived Growth Factor Receptor

PDGFR is an RTK activated in response to binding of its ligand, platelet-derived growth factor (PDGF), which has been shown to play a role in ALI, functioning as a chemotactic factor for inflammatory cells.[108] Overexpression of PDGF can induce inflammatory lung injury[109] and elevated concentrations of PDGF have been found in patients with ARDS.[110] Inhibition of the PDGF/PDGFR pathway by tyrosine kinase inhibitors attenuated lung injury in response to LPS and bleomycin, and may limit the fibroproliferative responses to ALI.[108,111]

PDGF has been shown to stimulate expression of MMPs in mesenchymal stem cells, allowing for traffic through basement membrane barriers.[112] It is also known that a fraction of PDGF is bound to the ECM and that thrombin (a proteinase) is responsible for cleavage and release of the membrane-bound form.[113] While there is no direct evidence to suggest that MMPs play a role in release or activation of PDGF, by analogy with other proteinases, it is possible that MMPs could also be involved in these processes.

## Conclusions

ARDS is a clinically important disease representing a large burden of ICU admissions and with few proven therapies beyond lung protective mechanical ventilation. The pathophysiology of ALI/ARDS involves an excessive inflammatory response resulting in accumulation of protein-rich pulmonary edema fluid through a disrupted alveolar-capillary barrier. MMPs and PTKs are novel participants in these processes, but their involvement is complex, encompassing multiple cell types and resulting in divergent effects along the path to lung injury. In the current manuscript, we have provided examples of how MMPs are able to trigger signaling pathways controlled by PTKs, both receptor and nonreceptor, promoting pro-inflammatory and injurious responses. These interactions are bidirectional and we have discussed how tyrosine kinase-dependent pathways can trigger secretion of MMPs and other proteinases. With these limitations in mind, further study is warranted. A better understanding of the role of MMPs and PTKs in ALI/ARDS may improve our understanding of the pathogenesis of this common lung disease, as well as provide new candidate prognostic biomarkers and targets for novel therapeutic approaches.

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